Guidelines for Nitrosamine Impurities in Drug substances and pharmaceutical drug Products Year 2025

Code:

Version No: 1/2025

Issue Date: / /2025

Effective date: / /2025

Table of Contents

1. Introduction and Background

Nitrosamine impurities have emerged as a significant quality and safety concern in the pharmaceutical industry since their initial detection in 2018. These impurities, classified as probable human carcinogens based on animal studies, present potential cancer risks to patients when present in pharmaceutical products above acceptable levels. The regulatory response to this issue has been global in scope, with health authorities worldwide including the U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), and other international regulators working collaboratively to establish comprehensive guidelines for industry. This guidance document synthesizes current regulatory expectations and provides practical recommendations for manufacturers to detect, control, and prevent nitrosamine impurities in active pharmaceutical ingredients (APIs) and finished drug products.

The discovery of nitrosamine contamination first occurred in angiotensin II receptor blockers (ARBs) like valsartan, losartan, and irbesartan, and subsequently extended to other medications including ranitidine, nizatidine, metformin, and various antibiotics. These findings led to widespread recalls and heightened regulatory scrutiny of pharmaceutical manufacturing processes worldwide. The concern stems from the fact that even at low levels, long-term exposure to certain nitrosamine impurities may increase cancer risk in humans.

Consequently, regulatory agencies have emphasized that marketing authorization holders bear ultimate responsibility for ensuring the quality and safety of their products, which includes implementing robust controls to prevent nitrosamine formation or contamination.

2. Types of Nitrosamine Impurities and Their Origins

Nitrosamine impurities in pharmaceuticals fall into two primary categories based on their structural characteristics and origin:

Small-molecule nitrosamines:

These are relatively low molecular weight compounds that do not share structural similarity with active pharmaceutical ingredients. They are often found across multiple different drug products. Common examples include:

- **N-nitrosodimethylamine (NDMA)**
- **N-nitrosodiethylamine (NDEA)**
- **N-nitrosomethylphenylamine (NMPA)**
- **N-nitrosodiisopropylamine (NDIPA)**
- **N-nitrosoisophenylethylamine (NIPEA)**
- **N-nitrosodibutylamine (NDBA)**
- **N-nitroso-N-methyl-4-aminobutyric acid (NMBA)**
- **And others**

Nitrosamine Drug Substance-Related Impurities (NDSRIs):

These impurities share structural similarity with the API or are derived from API fragments.

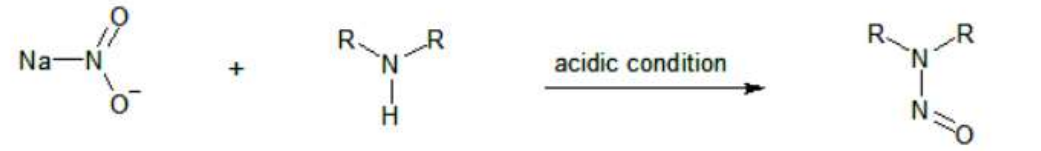
They are generally unique to each specific API and form through nitrosation of APIs or API fragments containing secondary or tertiary centers when exposed to nitrosating in favorable conditions.

The following examples include but not limited to NDSRIs:

Nitrosamine Name	Source
N-nitroso-atomoxetine	Atomoxetine
N-nitroso-duloxetine	Duloxetine
N-nitroso-fluoxetine	Fluoxetine
N-nitroso-methylphenidate	Methylphenidate

Root Causes and Formation Pathways

The formation of nitrosamine impurities occurs primarily through a chemical reaction between amines (secondary or tertiary) and nitrosating agents (typically nitrite salts under acidic conditions that form nitryl cation.



Sodium nitrite **Amine** **N-nitrosamine**

3. Risk Assessment Frameworks

3.1 Systematic Risk Evaluation

Manufacturers should conduct a comprehensive risk assessment for all chemically synthesized APIs and drug products to evaluate the potential for nitrosamine formation or contamination. This assessment should be science-based and systematically documented, considering all potential sources of nitrosamine impurities throughout the manufacturing process and supply chain. The risk is highest when secondary or tertiary amines and nitrosating agents are present simultaneously and under favorable conditions (e.g., acidic pH, elevated temperature, during processing or storage).

<u>Key elements of the risk assessment should include:</u>

API Manufacturing Process:

- Use of nitrite salts or nitrous acid in processes containing amine precursors.

-The use of sodium nitrite (or other nitrites) in the same equipment as amines without adequate cleaning in between could be a major cross-contamination risk.

- Presence of amine functional groups in APIs, degradants, intermediates, or raw materials.

- Secondary or Tertiary amines added as reagents or catalysts.

- Degradation of amide solvents (e.g., N,N-dimethylformamide) into secondary amines.

- Amine impurities in reagents or solvents.

- Use of nitrous acid to quench residual azide in the presence of precursor amines.

- Inadequate process optimization and control (temperature, pH, reagent addition sequence).

Drug Product Formulation and Storage:

- Reaction between APIs with amine functional groups and nitrite impurities in excipients

- Use of potable water containing nitrite impurities in manufacturing.

- Assessment of process conditions that could facilitate nitrosamine formation (presence of nitrites, acidic conditions, etc.).

- Leachates from container closure systems and secondary packaging components. (e.g. rubber stoppers in vials could be a potential source of nitrosating agents.)

- Manufacturing equipment as a source of nitrite or nitrosamine contamination.

Supply Chain Considerations:

- Vendor-sourced raw materials containing nitrosamine precursors

- Impurities in fresh solvents

- Cross-contamination at manufacturing sites

- Recovered materials (solvents, reagents, catalysts) containing residual amines or nitrosamine formation during recovery processes(e.g. the use of recovered solvents, especially from third-party recyclers, poses a significant and well-documented risk if not rigorously controlled).

- Inadequate cleaning between different materials or customers

Storage conditions:

Evaluation of potential nitrosamine formation during storage over the product's shelf life.

3.2 Prioritization Strategy

Products should be prioritized for evaluation based on the following factors (in descending order of importance):

1. **Medicines with known risks: Products similar to those previously found to contain nitrosamines (e.g., sartans, metformin)**
2. **High daily dose products: Products with higher maximum daily doses present greater potential exposure**
3. **Chronic treatments: Products intended for long-term use increase cumulative exposure risk**
4. **Large patient populations: Products used by many patients represent greater public health impact**
5. **Critical medicines: Products with limited alternatives require special consideration to avoid shortages**

Acceptable Intake Limits and Safety Assessment

4.1 Establishing Acceptable Intake Limits

Regulatory agencies recommend several approaches for determining AI limits:

Compound-specific carcinogenicity data:

When robust substance-specific animal carcinogenicity data exists, the TD50 (tumorigenic dose that induces tumors in 50% of test animals) should be calculated and used to derive a substance-specific limit for lifetime exposure as recommended in ICH M7(R2) guideline.

Predicted Carcinogenic Potency Categorization Approach (CPCA):

For NDSRIs lacking compound-specific data, AI limits can be assigned based on predicted carcinogenic potency categorization which categorizes nitrosamines into five potency categories based on their structural features:

Table: FDA's Carcinogenic Potency Categories and Corresponding AI Limits

Category	Acceptable Intake (AI)
1	26.5 ng/day
2	100 ng/day
3	400 ng/day
4	1500 ng/day
5	1500 ng/day

Read-across analysis:

Using robust carcinogenicity data from a structurally similar surrogate compound when substance-specific data is unavailable.

Default approach:

If the AI limit cannot be determined using the above approaches, AI limit may be recommended according to the FDA or EMA default AI limit for the most potent nitrosamines.

The FDA's default for nitrosamines without sufficient compund-specific data is 26.5 ng/day (the AI for Category 1)

. Analytical Testing and Specifications

5.1 Confirmatory Testing Strategies

When a risk assessment identifies potential nitrosamine formation or contamination, manufacturers should perform confirmatory testing using appropriately validated analytical methods. Key considerations for testing include:

Method validation: Analytical methods should demonstrate specificity (avoid matrix effect), excellent chromatographic separation, and highly sensitive detection capability (Cover the expected LOQ, 10 % of the Acceptable limit).

Testing scope: Confirmatory testing should be performed on at least three representative batches of drug product or API

Stability testing: Include testing of stability samples to evaluate potential nitrosamine formation over the product's shelf life

Method development: Consider published methods from regulatory agencies including FDA and European Official Medicine Control Laboratories (OMCL)

5.2 Specification Setting

If testing confirms the presence of a nitrosamine impurity above 10% of the acceptable intake limit, manufacturers should:

Establish specifications: Implement a specification limit for the nitrosamine impurity to ensure it remains at or below the recommended AI limit

Routine testing: Implement testing of each batch on release and stability samples for nitrosamine impurities for at-risk APIs or drug product with an impurity detected above 10% of the recommended AI limit

Control strategy: Develop an appropriate control strategy considering batch-to-batch variations

Batch rejection: Do not release any API or drug product batch containing levels of nitrosamine impurities above the recommended AI limit for distribution

The batch rejection rule applies at two key stages:

· At Release: Before a batch is released to the market, it must be tested (if it falls under a routine testing control strategy). If the test result shows a nitrosamine level at or above the AI, the batch must not be released. It is considered non-compliant and unsafe.

· During Shelf Life (Stability): The control strategy must ensure the impurity does not exceed the AI throughout the product's shelf life. If stability testing on a marketed batch shows that the nitrosamine level has risen to or above the AI before the expiry date, this typically triggers a batch recall. The product is no longer considered safe for its entire intended use period.

Mitigation and Control Strategies

6.1 Process Optimization and Design

Manufacturers should implement preventive measures to avoid nitrosamine formation through careful process design and optimization:

Route of synthesis evaluation: During process development, evaluate alternative synthetic routes that avoid conditions conducive to nitrosamine formation

Reagent selection: Avoid or replace amine bases, amide solvents, and nitrites whenever possible

Process conditions: Optimize reaction conditions (temperature, pH, reagent addition sequence) to minimize nitrosamine formation

Quenching modifications: Remove quenching steps from the primary reaction mixture or replace nitrites with alternative quenching agents

Purification steps: Incorporate purification steps capable of removing nitrosamine impurities when prevention is not fully achievable

6.2 Supply Chain Management

Robust supplier qualification and material controls are essential for preventing nitrosamine contamination:

Supplier audits: Conduct comprehensive audits of suppliers of raw materials, intermediates, and solvents

Material specifications: Establish appropriate specifications for raw materials regarding nitrite and amine content

Chain of custody: Request documented records of the name of the raw material manufacturer and its supplier and the roles of actual manufacturers

Recovered materials: Use recovered materials only in the same step or earlier steps of the same process from which they were collected to avoid cross-contamination

Water quality: Analyze water used in manufacturing for nitrites and nitrosamines and use purified water when necessary

6.3 Packaging and Storage Controls

Packaging selection and storage conditions can significantly impact nitrosamine formation:

Packaging evaluation: Assess container closure systems for potential to leach nitrosamines or nitrosating agents into the drug product

Alternative materials: Select packaging materials that do not contain nitrosamine precursors

Storage conditions: Establish appropriate storage conditions that minimize nitrosamine formation over time

Stability studies: Conduct comprehensive stability studies that include nitrosamine testing to verify control throughout the shelf life.

. Regulatory expectations:

EDA Recommended Timeline for Implementing Risk Assessments, Confirmatory Testing depending on the regulatory status of the drug product and the type of nitrosamine impurity at issue.

For drug substances:

All APIs listed in High risk APIs List that can form nitrosamine impurities should submit a detailed nitrosamine risk assessment through the specific link on the EDA website based on importation approval issued by central administration of pharmaceutical policies and market access.

For finished drug products submitted for registration or renewal evaluation:

For drug products containing metformin or sartans Comprehensive nitrosamine risk assessment should be included in the dossier from the date of guideline issue.

Drug products containing the rest of APIs listed in High risk APIs List that can form nitrosamine impurities, Comprehensive nitrosamine risk assessment should be included in the dossier from 1-1-2026.